Automation of a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer for Acquisition, Analysis, and E-mailing of High-Resolution Exact-Mass Electrospray Ionization Mass Spectral Data

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A system has been designed to automatically acquire high-resolution (>50,000 FWHM), exact-mass (mass measurement error ≤3 mmu) electrospray ionization mass spectra with a commercial Fourier transform ion cyclotron resonance mass spectrometer equipped with a high-field (9.4 tesla) superconducting magnet and a commercial autosampler. Upon the injection of each individual sample, the autosampler transmits a contact closure signal to the previously tuned and calibrated mass spectrometer to initiate data acquisition. A software package was designed to run off-line and to accept a sample list with input information for each of the samples. Then for each of the samples, the software automatically processes the acquired data, interprets the exact-mass data by correlating the observed masses with predicted masses computed from proposed elemental formulas, and then finally prints the spectra, peak lists, and exact-mass reports, and e-mails the exact-mass reports to the submitting chemists. With this automation package, large numbers of samples can be run unattended while obtaining exact masses for all the abundant ions in the spectra. Sample turnaround times are reduced with a corresponding increase in sample throughput. The performance of the system was evaluated with nearly 700 samples with a precalibrated instrument, without the presence of an internal standard. The system was found to be reliable and robust with a fitted standard deviation of 0.32 mmu and a small average systematic mass error of −0.28 mmu. Typical data acquired with the system have resolving powers >50,000 (FWHM) and mass errors <1.0 mmu. (J Am Soc Mass Spectrom 1999, 10, 1166–1173) © 1999 American Society for Mass Spectrometry

Fourier transform ion cyclotron resonance mass spectrometry (FTICR MS) has been shown to be a powerful technique for obtaining high-resolution exact-mass MS and MS^n data over the whole mass range of the spectrum [1]. The resolving power in FTICR MS increases linearly with increasing applied magnetic field with corresponding improvements in mass accuracy and signal-to-noise ratio [1, 2]. These desirable features can be routinely achieved with modern instruments equipped with high-field superconducting magnets. Even though very powerful data systems are used for data acquisition and data processing, electrospray ionization (ESI) FTICR experiments are generally conducted manually where single samples are infused one at a time. With this manual approach, the analysis of large numbers of samples is very time consuming, manpower inefficient, and hence not very cost effective. At our facility, chemists submit numerous samples of synthetic and natural origin to the analytical mass spectrometry laboratory for exact-mass measurements to confirm elemental formulas and thereby chemical structures. Often, for a variety of reasons, these materials failed to produce useful results by microanalysis. Many of these materials are pharmaceuticals and natural products and are very polar and thermally unstable and ESI is the ionization mode of choice for their analysis. To analyze the large numbers of samples efficiently under high-resolution exact-mass conditions, automation packages were designed to automatically acquire, process, interpret, and e-mail the ESI FTICR MS data. In this report, we describe the hardware and software details of a reliable and efficient system, presently in routine use,

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which completely integrates the automatic acquisition, processing, and interpretation of batches of FTICR MS data. With this integrated package, total automation is achieved for high-resolution exact-mass ESI FTICR MS data from the point of downloading sample information from a corporate database to the electronic delivery of the exact-mass report to the requesting chemist.

Some preliminary work in this field of automating ESI FTICR MS was described [3]. Very recently, several studies were reported using high performance magnetic sector mass spectrometers with fully automated acquisition, processing, and reporting of high-resolution exact-mass data with ESI using flow injection anaysis [4, 5] and with EI/CI (electron impact/chemical ionization) using a robotically controlled direct probe [6]. The significant differences between the performances of the high-field FTICR MS and magnetic sector systems will be discussed.

Experimental

The FTICR mass spectrometer used was a Bruker Daltonics APEX II equipped with a Bruker-Magnex passively shielded 9.4 tesla superconducting magnet (160 mm diameter bore), an external Analytica ESI source with API100 controller, a Hewlett-Packard Model 1100 HPLC system (Degasser, Pump, Diode Array Detector, Autosampler, Hand-Held Controller), and a UNIX based Silicon Graphics O2 Workstation data system. The external ESI source was operated with a grounded capillary sprayer needle mounted ~45° off-axis with nitrogen nebulizing gas at ambient temperature and 30 lb/in.^{2} and with nitrogen drying gas heated to 130 °C and flow rate of 20 L/h. The transfer capillary voltage was 2056 V on the source side and 90 V on the analyzer side. The skimmer voltage was 1.7 V. A hexapole ion guide in the external ESI source was used as an external trap to accumulate ions for times ranging from 0.5 to 5.0 s [7–10] before transfer to the FTICR MS INFINITY [11] analyzer cell. The transfer of ions from the ESI source hexapole ion guide to the analyzer cell is accomplished by electrostatic ion optics as has been previously described [12]. To trap the ions in the FTICR MS analyzer cell, the Sidekick ion accumulation method [13] and occasionally gated trapping (with and without trapping gas) [14] were used. Switching between Sidekick and gated trapping simply involved changing the values of electrostatic elements in the FTICR MS Infinity analyzer cell under computer control and varying the timing of these voltage changes, also under computer control. Typically 512 K data points were acquired. For low molecular weight pharmaceutical molecules of interest, resolving powers of 50,000 (FWHM) and absolute mass accuracies of <1.0 mmu (millimass unit) were routinely achieved. The instrument was calibrated with CsI, poly(ethylene glycol) bis(carboxymethyl) ether (average M_n ~ 600) or a peptide mixture containing angiotensin I and II, bradykinin, substance P, gramacidin, bombesin, actinomycin D, leucine enkephalin, and melittin. The stability of the instrument is remarkable in that mass accuracies <1.0 mmu can be achieved for a number of days without retuning and recalibrating the instrument. For this reason, external calibration was used for all measurements but the reference standard was run at the beginning and end of the series of samples to verify the stability and reproducibility of the measurements. The carrier solvent used was 1:1 water: acetonitrile (W:ACN) with a flow rate of 50 μL/min. To illustrate the automation methodology, a mixture of halogenated pharmaceuticals was analyzed which included chlorothiazide ($C_7H_6N_3O_4S_2Cl$, MW 294.9488), chloramphenicol ($C_{11}H_{12}N_2O_5Cl_2$, MW 322.0123), and dibromotyrosine ($C_9H_9NO_3Br_2$, MW 336.8949). These samples were purchased from Sigma Chemical (St. Louis, MO) and used as received. In addition, nearly 700 proprietary samples were analyzed with the automation instrumentation and the performance statistics for them were evaluated. The exact-mass errors reported correspond to the differences between the experimentally measured mass and the theoretical mass based upon the predicted elemental formula. All measured and corresponding theoretical masses were corrected for their ionic charges.

A Compaq Deskpro PC was used to download sample information from a corporate database and to communicate with the Silicon Graphics Workstation through the corporate intranet. PC programs to download and transfer the sample information were written in Visual Basic. Data processing using this sample information was performed under control of a script written in Tcl/Tk (Tool command language/Toolkit) [15]. Tcl/Tk is a platform independent, extendable, and embeddable programming language that was linked to Bruker's XMASS FTICR MS processing software. This link was accomplished by extending the Tcl scripting language with built-in commands that allow access to the XMASS command interpreter, enabling all XMASS commands to be executed from within Tcl scripts. Further versatility was added by creating built-in Tcl commands to permit access to all XMASS data parameters, as well as the raw and processed data vectors. In essence, XMASS could be controlled completely by the Tcl script. The Tcl scripts can also obtain information from XMASS, either directly via the built-in commands described above, or by causing XMASS to write data (i.e., peak lists) to a file on disk which could then be accessed by the Tcl script.

Results and Discussion

Automation System

The flow diagram for the automation of the ESI FTICR MS is illustrated in Figure 1. The system can be divided into two sections, one dealing with data acquisition and the other dealing with data processing. Each section can

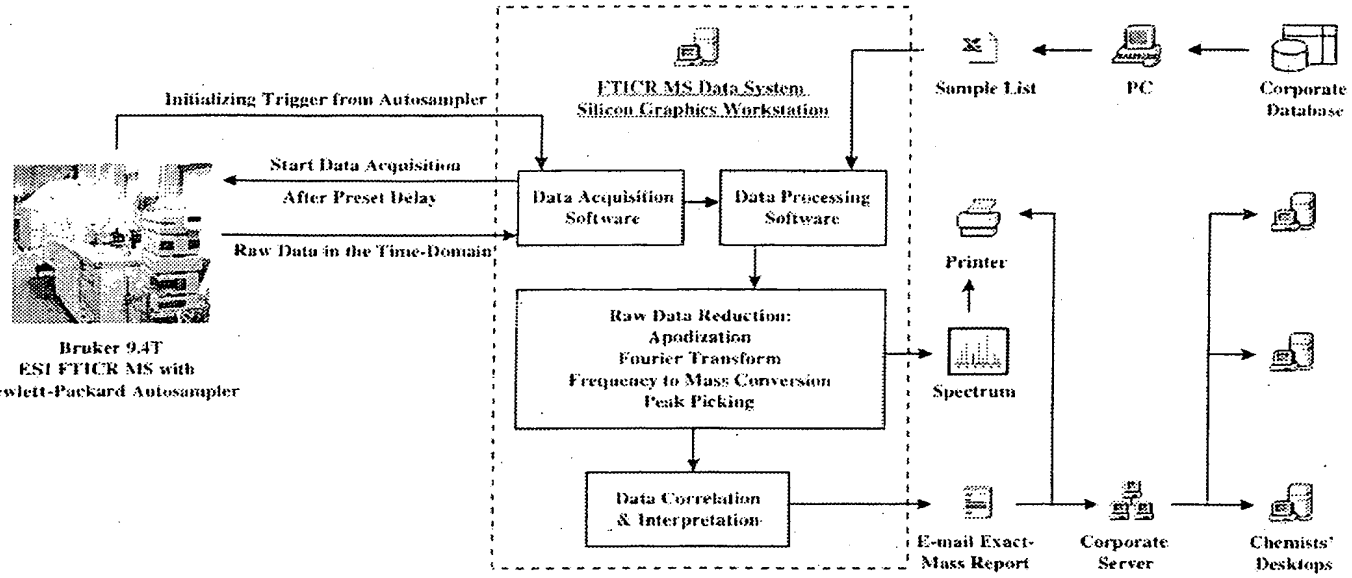


Figure 1. Schematic diagram of the hardware and software used to automate data acquisition, processing, and e-mailing of high-resolution exact-mass data, acquired in the ESI mode, using a Bruker 9.4T Apex II FTICR MS equipped with a Hewlett-Packard 1100 HPLC system including the HP1100 Autosampler.

function independently to acquire or process a batch of data. We now describe each of these sections individually.

Batch automatic data acquisition section. The autosampler upon injecting a 5 μL sample for flow injection analysis into the ESI source of the FTICR MS sends a TTL trigger to the mass spectrometer to initiate data acquisition after a preset delay time necessary for the sample to flow into the ESI source, typically in our system after a delay of about 30 s. The pretuned and precalibrated instrument acquires and sums 30 spectra for a total acquisition time of about 30 s. This raw time-domain data is stored for future processing. After a total time of 2.0 min the next sample is injected. This later delay of about 1.0 min is used to clean the autosampler, tubing and source of any residual analyte, consequently cross contamination of later samples is reduced. This process is repeated until all the samples placed in the autosampler and listed in the Hand-Held Controller are run. A maximum of 100 samples can be run in one batch with the Hewlett-Packard Model 1100 Autosampler.

Batch automatic data processing section. The data reduction, analysis, and e-mailing steps described below are automatically repeated for all the samples analyzed in a given batch.

(a) Sample list generation. Sample information is downloaded directly from a corporate database and a sample list is automatically generated on a PC in the Microsoft Excel spreadsheet format. The sample list is transferred as a tab delimited text file through the corporate intranet to the Silicon Graphics Workstation. The sample list information (chemist name, notebook number, request number, predicted elemental formula, autosampler vial number, MS log book number) is used as header information for all generated reports and the predicted elemental formula is used for mass spectral interpretation. Each component predicted to be present in a sample is entered individually as a separate line entry in the sample list with the same vial number.

(b) Raw data reduction. The raw summed time-domain spectra are automatically processed by preset operating parameters. The processes are apodization of the time-domain data, generally selected as a centered sine bell function, fast Fourier transform with zero filling, frequency to mass conversion, and peak picking. Options for automatic printout of the spectrum and peak list are available. Figure 2 is an example of an automatically acquired spectrum of a mixture of three halogenated pharmaceuticals in the ESI negative ion mode. Note that the exact masses and isotopic distributions are consistent with the predicted values for all the abundant ions.

(c) Data correlation/interpretation. This module compares the exact masses from the list of picked peaks with those of the possible molecular ion adducts predicted to be formed from the expected elemental formula indicated in the Sample List for the sample. Table 1 lists the possible molecular ion adducts that can be formed under ESI conditions in both the positive and negative ionization modes. Also tabulated for each possible adduct is the mass change due to adduct

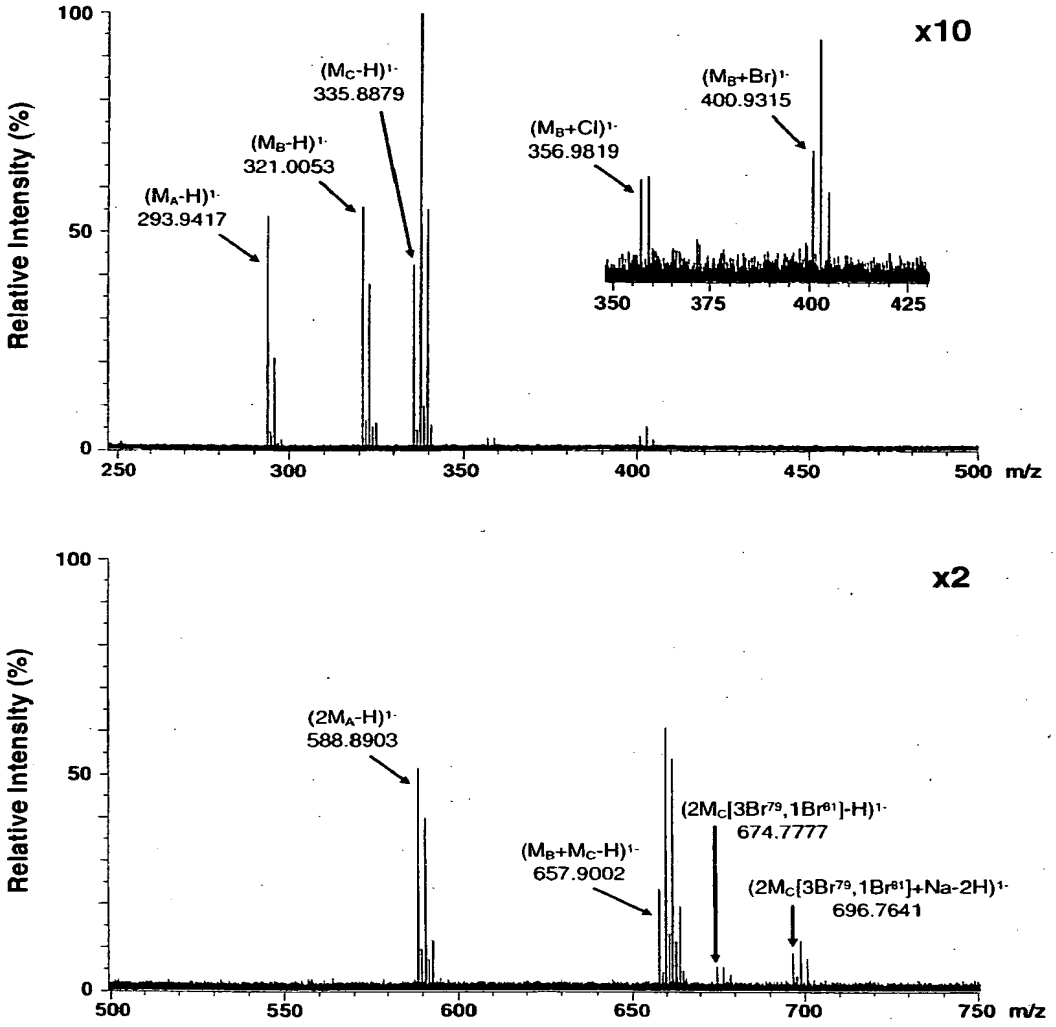


Figure 2. Expanded high-resolution exact-mass spectrum automatically acquired in the ESI negative ion mode by FTICR mass spectrometry for a mixture of the pharmaceuticals chlorothiazide (M_A), chloramphenicol (M_B), and dibromotyrosine (M_C). All monoisotopic masses below *m/z* 600 were automatically selected and identified by the Tcl/Tk data correlation/interpretation program. Ions above *m/z* 600 were not automatically assigned because Table 1 is designed for computations of only homodimers and not heterodimers (*m/z* 657.9007) and for computations of only monoisotopic masses which were not observed for the two weak distributions above *m/z* 670.

formation and the charge of the ion. This information is used by the Tcl/Tk macro to compute the exact masses of the molecular ion adducts. Table 1 can be easily customized for specialized problems and can also include possible artifact ions, starting materials, expected impurities, etc. The algorithm determines the polarity of the ESI experiment from the value of the trapping plate parameters, viz., positive (negative) trap plate voltages correspond to positive (negative) ions. An option for automatic printout of the exact-mass report is available. Also, a summary report of the test results for all the samples is generated automatically for bookkeeping purposes.

(d) E-mailing of exact-mass report. An alias file is set up to link submitter names with their e-mail addresses. The Tcl/Tk macro calls up an e-mail macro which attaches the exact-mass report as a text file and transmits it to the submitting chemist via the corporate intranet. Figure 3 illustrates a typical e-mailed exact-mass report using Novell GroupWise as displayed in Microsoft Notepad for the spectrum illustrated in Figure 2. The report lists the name, charge, and exact-mass of the predicted molecular ion adduct, the correlated observed mass, the mass error in mmu and ppm and the relative intensity of the ion. Only consistent results (absolute exact-mass errors ≤3 mmu) are e-mailed. Absence of the predicted exact-mass indicates inconsistent (absolute mass error >3 mmu) or inconclusive (insufficient signal) results.

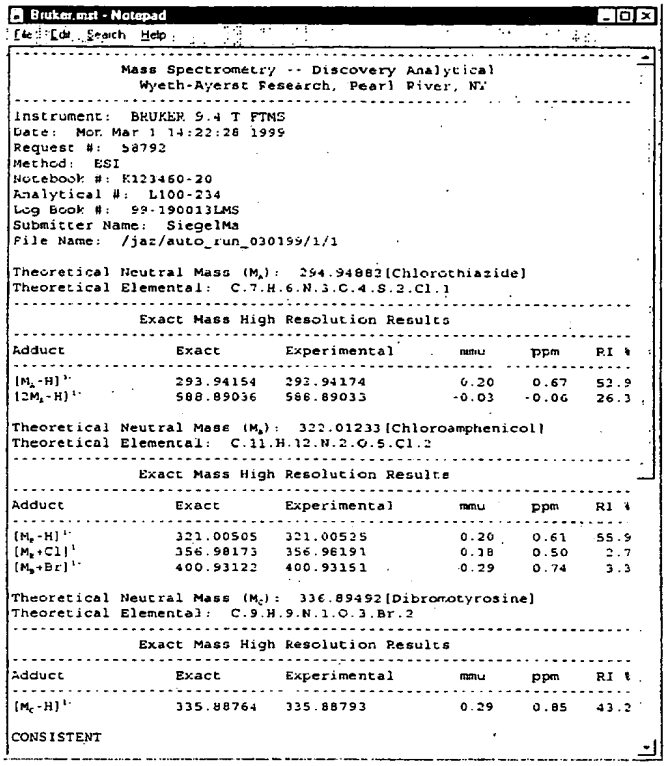
Table 1. Monoisotopic exact masses of molecular ion adducts often observed in ESI mass spectra

Ion name[a]	Ion mass[a]	Charge
1. Positive ion mode		
M + 3H	M/3 + 1.007276	3+
M + 2H + Na	M/3 + 8.334590	3+
M + H + 2Na	M/3 + 15.7661904	3+
M + 3Na	M/3 + 22.989218	3+
M + 2H	M/2 + 1.007276	2+
M + H + NH_4	M/2 + 9.520550	2+
M + H + Na	M/2 + 11.998247	2+
M + H + K	M/2 + 19.985217	2+
M + ACN + 2H[b]	M/2 + 21.520550	2+
M + 2Na	M/2 + 22.989218	2+
M + 2ACN + 2H[b]	M/2 + 42.033823	2+
M + 3ACN + 2H[b]	M/2 + 62.547097	2+
M + H	M + 1.007276	1+
M + NH_4	M + 18.033823	1+
M + Na	M + 22.989218	1+
M + K	M + 38.963158	1+
M + CH_3OH + H	M + 33.033489	1+
M + ACN + H	M + 42.033823	1+
M + 2Na − H	M + 44.971160	1+
M + ACN + Na	M + 64.015765	1+
M + 2K − H	M + 76.919040	1+
M + DMSO + H	M + 79.02122	1+
M + 2ACN + H	M + 83.060370	1+
2M + H	2M + 1.007276	1+
2M + NH_4	2M + 18.033823	1+
2M + Na	2M + 22.989218	1+
2M + K	2M + 38.963158	1+
2M + ACN + H	2M + 42.033823	1+
2M + ACN + Na	2M + 64.015765	1+
2M + 3H_2O + 2H[b,c]	M + 28.02312	2+
2. Negative ion mode		
M − 3H	M/3 − 1.007276	3−
M − 2H	M/2 − 1.007276	2−
M − H	M − 1.007276	1−
M + Na − 2H	M + 20.974666	1−
M + Cl	M + 34.969402	1−
M + K − 2H	M + 36.948606	1−
M + FA − H	M + 44.998201	1−
M + HAc − H	M + 59.013851	1−
M + Br	M + 78.918885	1−
M + TFA − H	M + 112.985586	1−
2M − H	2M − 1.007276	1−
2M + FA − H	2M + 44.998201	1−
2M + HAc − H	2M + 59.013851	1−
3M − H	3M − 1.007276	1−

[a]M is the MW, ACN is acetonitrile, DMSO is dimethylsulfoxide, FA is formic acid, HAc is acetic acid, TFA is trifluoroacetic acid.
[b]Observed with high source pressures.
[c]Observed with sulfonyl amides RSO_2NHR'.

Performance of Automation System

The performance of the automated ESI FTICR MS system was evaluated by repeated injection of a single sample with automated analysis and by single injection with automated analysis of 694 different preselected polar samples. (Less polar samples were automatically analyzed by exact-mass high-resolution EI/CI using an automated direct probe on a high performance magnetic sector mass spectrometer [6].)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              Wyeth-Ayerst Research, Pearl River, NY
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Instrument:  BRUKER 9.4 T FTMS
Date:  Mon Mar 1 14:22:28 1999
Request #:  58792
Method:  ESI
Notebook #: K123460-20
Analytical #:  L100-234
Log Book #:  99-190013LMS
Submitter Name:  SiegelMa
File Name:  /jaz/auto_run_030199/1/1

Theoretical Neutral Mass (M1):  294.94882[Chlorothiazide]
Theoretical Elemental:  C.7.H.6.N.3.O.4.S.2.Cl.1
-------------------------------------------------------------------------------
                  Exact Mass High Resolution Results
-------------------------------------------------------------------------------
Adduct          Exact       Experimental      mmu      ppm     RI %
-------------------------------------------------------------------------------
[M1-H]1-        293.94154   293.94174         0.20     0.67    52.9
[2M1-H]1-       588.89036   588.89033        -0.03    -0.06    26.3

Theoretical Neutral Mass (M2):  322.01233[Chloroamphenicol]
Theoretical Elemental:  C.11.H.12.N.2.O.5.Cl.2
-------------------------------------------------------------------------------
                  Exact Mass High Resolution Results
-------------------------------------------------------------------------------
Adduct          Exact       Experimental      mmu      ppm     RI %
-------------------------------------------------------------------------------
[M2-H]1-        321.00505   321.00525         0.20     0.61    55.9
[M2+Cl]1-       356.98173   356.98191         0.18     0.50     2.7
[M2+Br]1-       400.93122   400.93151         0.29     0.74     3.3

Theoretical Neutral Mass (M3):  336.89492[Dibromotyrosine]
Theoretical Elemental:  C.9.H.9.N.1.O.3.Br.2
-------------------------------------------------------------------------------
                  Exact Mass High Resolution Results
-------------------------------------------------------------------------------
Adduct          Exact       Experimental      mmu      ppm     RI %
-------------------------------------------------------------------------------
[M3-H]1-        335.88764   335.88793         0.29     0.85    43.2

CONSISTENT
```

Figure 3. An example of an e-mailed exact-mass report viewed as a Microsoft Notepad text file for the mixture analyzed by ESI FTICR mass spectrometry and illustrated in Figure 2. The content of the report includes the identified molecular ion adduct peaks (Adduct), the predicted (Exact), and observed (Experimental) exact masses, the mass error (Experimental Mass − Exact Mass) reported in millimass units (mmu) and parts per million (ppm), and the relative intensity of the peaks (RI %). Because the reported absolute mass errors are less than 3 mmu, the observed data confirm the predicted elemental formulas and the results are deemed to be "CONSISTENT" with the proposed structures.

The reliability of the system was demonstrated by repeated flow injection analysis of dibromotyrosine (MW 336.8949) in the negative ionization ESI mode when calibrated externally and internally with poly(ethylene glycol) bis(carboxymethyl) ether oligomers with average MW of about 600 Da. Table 2 summarizes the results of the 10 analyses in each calibration mode for the observed $[M - H]^{1-}$ and $[2M - H]^{1-}$ molecular ions. The observed signal-to-noise ratios for the observed molecular ions for each injection was greater than 100:1 with resolving powers of about 90,000 for the $[M - H]^{1-}$ and 45,000 for the $[2M - H]^{1-}$. With external calibration, the mass accuracy, as measured by the average mass errors, was higher for the lower mass ion while with internal calibration the mass accuracies were about the same for both ions. The precision of the measurements, as indicated by the low standard deviation of the average error, is quite high for both external and internal calibration experiments. It is important to note that the high accuracies achieved with external calibration are

Table 2. Ten repeated injections and automated FTICR MS exact-mass measurements of dibromotyrosine[a] with external and internal standards[b]

	Measured mass	Δ[c]		Measured mass	Δ[c]	
	Da	mmu	ppm	Da	mmu	ppm
External calibration[b]						
1	335.88771	0.07	0.20	672.78335	0.79	1.17
2	335.88769	0.05	0.14	672.78338	0.82	1.21
3	335.88775	0.11	0.32	672.78336	0.80	1.18
4	335.88773	0.09	0.26	672.78341	0.89	1.26
5	335.88777	0.13	0.38	672.78333	0.77	1.14
6	335.88779	0.15	0.43	672.78357	1.01	1.50
7	335.88772	0.08	0.23	672.78328	0.72	1.06
8	335.88775	0.11	0.32	672.78331	0.75	1.11
9	335.88779	0.15	0.43	672.78356	1.00	1.48
10	335.88790	0.26	0.76	672.78378	1.22	1.81
Average	335.88776	0.12	0.35	672.78343	0.88	1.29
Std. Deviation	0.000059	0.06	0.17	0.000157	0.16	0.23
Internal calibration[b]						
1	335.88769	0.05	0.14	672.78293	0.37	0.54
2	335.88764	0.00	−0.01	672.78249	−0.07	−0.11
3	335.88758	−0.06	−0.19	672.78239	−0.17	−0.26
4	335.88783	0.19	0.55	672.78254	−0.02	−0.04
5	335.88773	0.09	0.26	672.78275	0.19	0.28
6	335.88760	−0.04	−0.13	672.78260	0.04	0.05
7	335.88783	0.19	0.55	672.78255	−0.01	−0.02
8	335.88770	0.06	0.17	672.78226	−0.30	−0.45
9	335.88774	0.10	0.29	672.78278	0.22	0.32
10	335.88759	−0.05	−0.16	672.78250	−0.06	−0.10
Average	335.88769	0.05	0.15	672.78258	0.02	0.02
Std. Deviation	0.000092	0.09	0.27	0.000196	0.20	0.29

[a]The predicted masses for dibromotyrosine: $[M - H]^{1-}$ = 335.88764, $[2M - H]^{1-}$ = 672.78256.
[b]The reference compound was poly(ethylene glycol) bis(carboxymethyl) ether, average M_n ~ 600.
[c]Δ = Measured mass − predicted mass.

sufficient to confirm a proposed elemental formula and that internal calibration did improve the measured accuracies but not significantly enough to be required for confirmation of proposed elemental formulas. This apparently is a unique feature when using high-field superconducting magnets in FTICR MS in the wide mass scanning mode. Even greater improvements in mass accuracy are expected with internal standards in the heterodyne narrow mass range scanning mode as illustrated by Shi et al. [16].

The mass error distribution for the automated analysis of 694 samples by ESI FTICR MS is illustrated in Figure 4A. The results are overlayed with a fitted Gaussian curve which has a standard deviation of 0.32 mmu and a center mass of −0.28 mmu, corresponding to the average systematic error in the measurements. The mass error distribution is relatively sharp with a small percentage of points in the tail of the fitted Gaussian distribution. These larger errors are due either to low signal-to-noise ratio or samples that were inconsistent with the proposed structures. (The standard deviation when computed to include all the data is 0.73 mmu.) The distributions of the errors when reported in ppm as a function of the percentage of the 694 samples were as follows: 0–1 ppm were 62.1%, 1–2 ppm were 28.2%, 2–3 ppm were 5.5%, and >3 ppm were 4.2%. Figure 4B illustrates the distributions of the average absolute error and standard deviation as a function of measured mass. These errors tend to increase with increasing mass due to space charge effects [17]. Automated EI/CI exact-mass high-resolution measurements in the peak matching mode on a high performance magnetic sector instrument on about 500 samples produced a similar average systematic mass error (−0.47 mmu), a wider standard deviation (1.61 mmu) while the error distribution as a function of mass was constant [6]. The significant differences between the performances of the automated FTICR MS and automated magnetic sector systems are the ability of the high-field FTMS system to acquire reliable exact-mass data for long periods of time without the presence of internal standards, with improved mass accuracy and without sacrificing sensitivity for resolving power.

Conclusions

We have developed a batch processing package for automated acquisition, processing, interpretation, and e-mailing of high-resolution exact-mass ESI data acquired by direct infusion on a commercial high-field 9.4 tesla FTICR mass spectrometer. This package permits reliable unattended operation of the instrument for

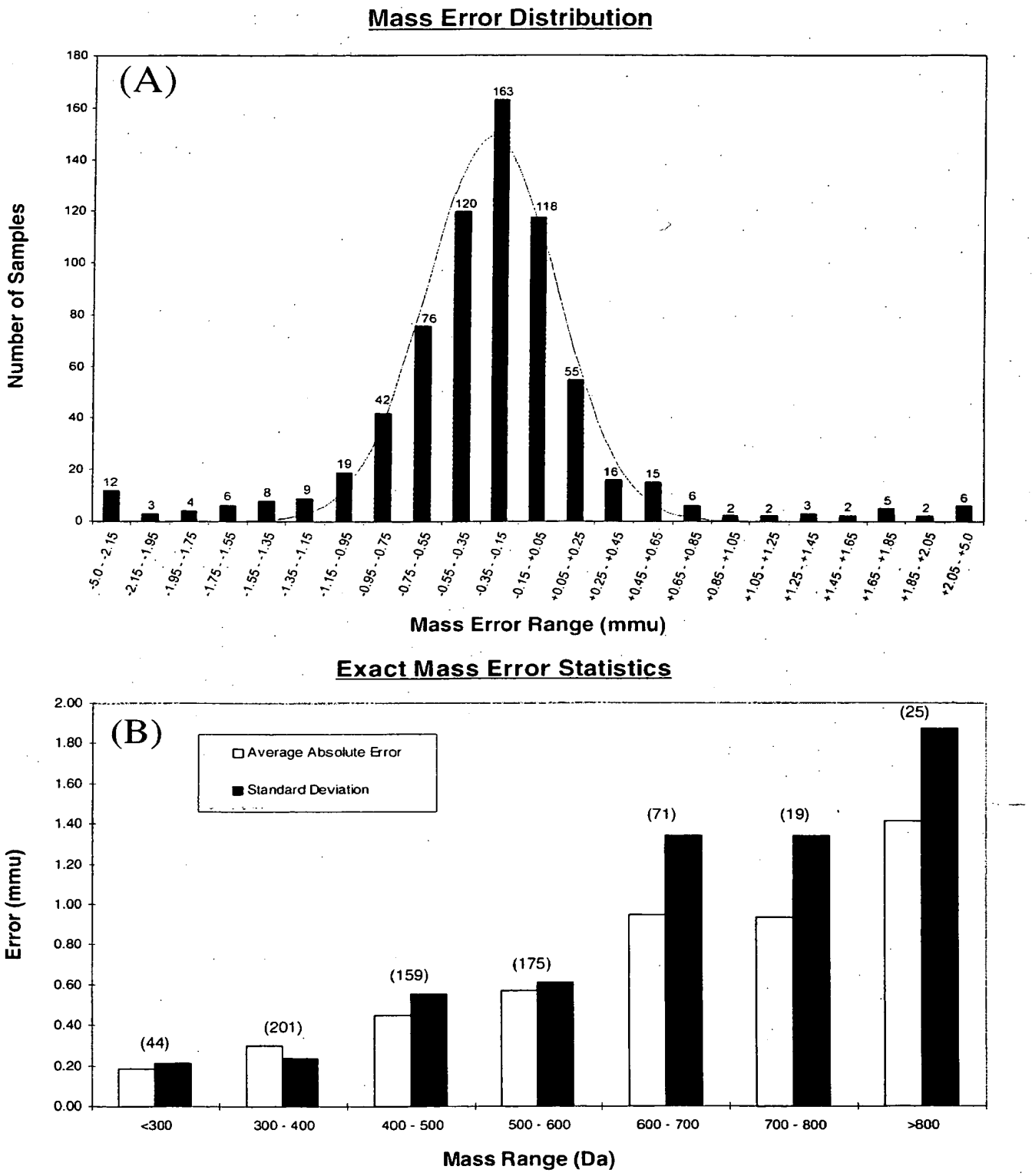

Figure 4. Exact-mass error analysis for 694 samples analyzed by high-resolution high-field FTICR MS by ESI flow injection analysis with external calibration utilizing automated data acquisition and analysis. (A) Exact-mass error distribution and Gaussian fit as a function of mass error range with a standard deviation of 0.32 mmu and an average error of −0.28 mmu. The numbers above the bars correspond to the number of samples in each mass error range. (B) Exact-mass error statistics for the average absolute error and standard deviation as a function of mass range. The numbers above the bars correspond to the number of samples in each mass range. (See text for discussion.)

large numbers of samples and the efficient acquisition and analysis of the data, thereby increasing the productivity of the system. Typically with this system, resolving powers >50,000 (FWHM) and mass measurement errors <1.0 mmu and/or <1.0 ppm are routinely achieved with ions of moderate abundance for pharmaceuticals with molecular weights ranging from 250 to 700 Da with external calibration. Future extensions of the software include automated sequential acquisition, processing, and e-mailing of MS, MS^n [18], and LC MS data for both electrospray and atmospheric pressure chemical ionization modes (with either internal or external calibration) and automated instrument shutdown.

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